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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,132	02/23/2007	John W. Adams	AREN-060 (060.US2.PCT)	9424

65643 7590 09/08/2010

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
09/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,132	ADAMS ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *136-154 and 156-163* is/are pending in the application.

4a) Of the above claim(s) *144-154* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *136-143 and 156-163* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04/27/2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/21/2010 has been entered. Claims 136-154 and 156-163 are pending. Claims 136-143 and 156-163 are currently under consideration. All other claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Request for Interview

It is noted that that Applicants requested a telephonic interview in the response filed on 04/27/2010. Applicants may call the examiner at any time to schedule a telephonic interview with the examiner.

Withdrawn Objections and/or Rejections

The rejection of claims 136-143 and 155-157 under 35 U.S.C. §112, second paragraph is withdrawn in view of amended claims.

Drawings

The drawing, Fig. 2, which submitted on 04/27/2010 is accepted by the examiner.

Claim Rejections under 35 USC § 112, 1st paragraph

(i). The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii). Claims 136-143 and 156-163 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 136 and new claim 160 recite a limitation, "wherein said G protein-coupled receptor has constitutive activity", which introduces new matter. The specification (page 133, paragraph [0553]) discloses that overexpression of RUP40 in cardiomyocytes stimulated increased IP3accumulation and the overexpressed RUP40 therefore manifested a level of constitutive Gq coupling activity under the conditions of the assay. However, there is no requirement for the GPCR used in the method to be overexpressed. Thus, the subject matter in the amendment is broader than that

disclosed in the specification. All other claims depend from claims 136 or 160, either directly or indirectly.

(iii). Claims 136-143, and 156-163 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. New claims 158 and 159 are also rejected on the same basis.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claim 136 is drawn to a method of identifying a compound capable of inhibiting cardiomyocyte hypertrophy, comprising (a) contacting a candidate compound with a G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1346 of SEQ ID NO: 2, wherein said G protein-coupled receptor has constitutive activity, and wherein said G protein-coupled receptor is

present on a cell or an isolated membrane thereof, (b) determining that the compound inhibits signaling by said G protein-coupled receptor, and (c) determining if the compound inhibits hypertrophy of a heart cell. Claim 160 is drawn to a method of identifying a compound capable of inhibiting cardiomyocyte hypertrophy, comprising (a) contacting a candidate compound with a G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1346 of SEQ ID NO: 2, wherein said G protein-coupled receptor has constitutive activity, and wherein said G protein-coupled receptor is present on a cell or an isolated membrane thereof, (b) determining that the compound inhibits signaling by said G protein-coupled receptor, wherein said compound is capable of inhibiting hypertrophy of a cardiomyocyte cell. All other claims depend from either claim 136 or claim 160, either directly or indirectly. The claims encompass a method of using a genus of GPCR polypeptides comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1346 of SEQ ID NO: 2. The claims do not require that GPCR variants or homologues possess any particular biological activity, nor any particular conserved structure, nor other disclosed distinguishing feature. Thus, the claims are overly broad.

The specification discloses the human RUP40 GPCR polypeptides set forth in SEQ ID NO: 2 and the nucleic acid sequence of SEQ ID NO: 1 encoding the polypeptide. The specification also discloses two orthologs of human RUP40, rat RUP40 and mouse RUP40 (see, e.g., paragraph [0038]). The specification asserts that RUP40 is highly expressed in heart, lung, aorta and adipose (page 68, paragraph [0320]) and that over-

expression of RUP40 in cardiomyocytes result in increased IP3 accumulation (Example 14), manifested a level of constitutive Gq coupling activity, and a subsequent increase in atrial natriuretic factor (ANF) expression and hypertrophy (page 13, paragraph [0016]; Example 15).

However, the specification fails to provide sufficient guidance and/or working examples with respect to how to make and use the claimed invention. The specification fails to disclose a biological ligand or an active agonist that activates the human RUP40 set forth in SEQ IUD NO: 2. Moreover, the human RUP40 is not disclosed as being constitutive active. Instead, as noted above, the specification discloses that over-expression of RUP40 in cardiomyocytes result in increased IP3 accumulation (Example 14) and manifested a level of constitutive Gq coupling activity. Without a known ligand/agonist or overexpression of the human RUP40 in cardiomyocytes, one skilled in the art would not be able to identify a compound that inhibits the signaling of human RUP40 and inhibits cardiomyocyte hypertrophy. Moreover, claim 136, (a), recites wherein said G protein-coupled receptor is present on a cell or an isolated membrane thereof", whereas step (c) of claim 136 recites "determining if the compound inhibits hypertrophy of a heart cell". It is noted that inhibiting cardiomyocyte hypertrophy may be determined in a cardiomyocyte cell, not any kind of cell as recited in the claim.

The specification asserts that three variants of human RUP40 of SEQ ID NO: 2 were envisioned (page 15, paragraph [0056]). However, there is no description of other

mutational sites that exist in nature, and there is no description of how the structure of the polypeptide of SEQ ID NO: 2 relates to the structure of different variants. The general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of other unknown variants having concordant or discordant functions. The nature of variants is such that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others.

The prior art (see, e.g., U.S. Patent No. 7,049,096) teaches a human GPCR, which comprises amino acids 991 to 1346 of SEQ ID NO: 2. However, the prior art does not teach the ligand of the human RUP40 and does not provide compensatory structural or correlative teachings to enable one skilled in the art to make the encompassed GPCR variants and homologues that can be used in the instant claimed method.

It is unpredictable whether a GPCR that has 95% sequence identity to amino acids 991 to 1346 of SEQ ID NO: 2 shares the same property of RUP40 GPCR of SEQ ID NO: 2 because the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the recited genus of GPCR variants and homologues. There is no description of the conserved regions that are critical to the structure and function of the genus recited. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of

structure to function. It would take undue experimentation for one skilled in the art to practice the instantly claimed invention.

Accordingly, in view of the various factors, the instant disclosure fails to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

(iii). Response to Applicants' argument

On the third paragraph of page 7 of Applicants' response filed on 04/27/2010, Applicants argue that RUP40 does not have to be modified in order to be used in the assay to provide a phenotype. Applicants argue that the specification on page 133 discloses that RUP40 manifested a level of constitutive Gq coupling activity when used in the assay described in Example 14 of the application. Applicants also argue that this is consistent with the results discussed in Example 15, which show that wild type RUP40 causes a cellular phenotype if it is expressed in a cell. Applicants argue that the method may be done without an agonist for the receptor, and without making a change to the receptor to make it constitutively active.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the human RUP40 is not disclosed as being constitutive active. Instead, the specification discloses that over-expression of RUP40 in cardiomyocytes result in increased IP3 accumulation (Example 14), manifested a level of constitutive Gq

coupling activity, and a subsequent increase in atrial natriuretic factor (ANF) expression and hypertrophy (page 13, paragraph [0016]; Example 15). However, the claims do not recite the limitation "over-expression of RUP40 in cardiomyocytes" and the conditions used in the assay described in Example 15.

On the 4th paragraph of page 7 and last paragraph of page 8 of Applicants' response filed on 04/27/2010, Applicants argue that Applicants argue that even if functional variants cannot be predicted with 100% accuracy by design alone, a functional variant can be readily identified by expressing the variant in a cell to determine if it has constitutively or cause a phenotype. Applicants argue that a method would not required undue experimentation.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the claims do not require that the variants of the human RUP40 set forth in SEQ ID NO: 2 possess any particular biological activity nor any particular conserved structure. The recited limitation "wherein said G protein-coupled receptor has constitutive activity" does not represent a meaningful functional limitation because the human RUP40 is not disclosed as being constitutive active. Instead, the specification discloses that over-expression of RUP40 in cardiomyocytes result in increased IP3 accumulation (Example 14), manifested a level of constitutive Gq coupling activity, and a subsequent increase in atrial natriuretic factor (ANF) expression and hypertrophy (page 13, paragraph [0016]; Example 15). Thus, it would require undue experimentation

to make and use the claimed methods because one would have to determine first whether a particular GPCR that has at least 95% identity to amino acids 991 to 1364 of SEQ ID NO: 2 can be used to screen for an inhibitor of hypertrophy of a heart cell.

Claim Rejections under 35 U.S.C. §102 (b)

(i). The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(ii). Claims 160 and 162 are rejected under 35 U.S.C. 102(b) as being anticipated by Feder et al. (US Patent No. 7,049,096 B2, May 23, 2006; filing date: 04/11/2002).

Feder et al. teach a human GPCR polypeptide comprising amino acids 991 to 1346 of SEQ ID NO: 2 of the present invention (see sequence alignment attached to the office action mailed on 06/01/2009). Feder et al. teach a method of identifying an antagonist of the GPCR polypeptide, which comprises expressing the receptor polypeptide on the cell surface, contacting the cell with a test compound, and determining if the test compound inhibits a functional response of the GPCR polypeptide (see, e.g., column 203, lines 39-56). Feder et al. also teach use a report protein (bottom of column 205; column 206, begging at the 2nd paragraph). Since the GPCR polypeptide comprises the amino acids 991 to 1346 of SEQ ID NO: 2 of the present invention and Feder et al. teach the same

identical method steps recited in claim 136, the test compound identified by the method of Feder et al. would be capable of possess the properties recited in the claims.

Claim Objections for Minor Informalities

Claims 136-143 and 155-163 are objected to because they recite non-elected species (species other than hypertrophic cardiomyopathy). Appropriate correction is required.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

September 3, 2010